AMENDMENT

In the Claims:

Please amend the claims as follows:

1. (Original) (Original)A polynucleotide construct comprising a region encoding a siRNA operably linked to an externally controllable promoter.

2. (Original) (Original) The construct of claim 1, further defined as a vector.

3. (Original) (Original) The construct of claim 2, wherein the vector is a lentiviral vector, a retroviral vector, an MLV vector, an AAV vector, a plasmid vector or an adenoviral vector.

4. (Original) The construct of claim 1, wherein the externally controllable promoter is a repressible promoter whereby expression of the encoded siRNA can be downregulated by means of an externally applied agent.

5. (Original) The construct of claim 4, wherein expression of the encoded siRNA can be downregulated by means of an externally applied drug.

6. (Original) The construct of claim 1, wherein the repressible promoter is regulated by a Tet repressor.

7. (Original) The construct of claim 1, wherein the repressible promoter is defined as further comprising at least one *tetO* sequence.

8. (Original) The construct of claim 1, wherein the repressible promoter is regulated by the lacI repressor.

9. (Original) The construct of claim 1, wherein the repressible promoter is from the gene of ANB1, HEM 13, ERG 11, OLE 1, GAL1, GAL10, ADH2, or TET^R.

10. (Original) The construct of claim 1, wherein the externally controllable promoter is an inducible promoter whereby expression of the encoded siRNA can be upregulated by means of an externally applied agent.

11. (Original) The construct of claim 10, wherein the inducible promoter is inducible by Cu^{+2}, Zn^{2+}, tetracycline, tetracycline analog, ecdysone, glucocorticoid, tamoxifen, or an inducer of the lac operon.

12. (Original) The construct of claim 11, wherein said promoter is inducible by ecdysone, glucocorticoid, or tamoxifen.

13. (Original) The construct of claim 10, wherein said inducible promoter is a phage inducible promoter, nutrient inducible promoter, temperature inducible promoter, radiation inducible promoter, metal inducible promoter, hormone inducible promoter, steroid inducible promoter, antibiotic inducible promoter, or combination thereof.

14. (Original) The construct of claim 13, wherein said radiation inducible promoter is a fos promoter, a jun promoter, or an erg promoter.

15. (Original) A system for controlling gene expression comprising:

(a) one or more polynucleotide constructs in accordance with claim 1;

(b) a compound or reagent that may be administered to the cell that directly or indirectly controls the expression of the siRNA.

16. (Original) The system of claim 15, further defined as comprising:

a) a regulatable siRNA-expression construct comprising an siRNA encoding nucleic acid segment potentially under the control of a regulatable promoter region; and

b) a polynucleotide encoding a regulatable polypeptide regulator of the regulatable siRNA-expression construct.

17. (Original) The system of claim 15, wherein an excisable fragment is located between the segment and the regulatable promoter region.

18. (Original) The system of claim 17, wherein the expression of an agent that excises said excisable fragment is under the control of a tissue-specific promoter.

19. (Original) The system of claim 16, wherein the regulatable siRNA-expression construct is an integrating viral vector.

20. (Original) The system of claim 18, wherein the integrating viral vector is a lentivirus, a retrovirus, or an adeno-associated virus.

21. (Original) The system of claim 19, wherein the integrating viral vector is a lentivirus.

22. (Original) The system of claim 16, wherein the regulatable siRNA-expression construct comprises a marker to assay for integration.

23. (Original) The system of claim 16, wherein the regulatable promoter region comprises a nucleic acid segment that negatively regulates transcription from the promoter.

24. (Original) The system of claim 16, wherein the nucleic acid segment that negatively regulates transcription from the promoter is a *tet* operator.

25. (Original) The system of claim 22, wherein the regulatable polypeptide regulator is capable of binding the *tet* operator.

26. (Original) The system of claim 18, wherein the tissue specific promoter is liver fatty acid binding (FAB) protein gene promoter, insulin gene promoter, transphyretin promoter, α1-antitrypsin promoter, plasminogen activator inhibitor type 1 (PAI-1) promoter, apolipoprotein AI promoter, LDL receptor gene promoter, myelin basic protein (MBP) gene promoter, glial fibrillary acidic protein (GFAP) gene promoter, opsin promoter, LCK promoter, CD4 promoter, keratin promoter, myoglobulin promoter, or neural-specific enolase (NSE) promoter.

27. (Original) The system of claim 16, wherein the polynucleotide is under the control of a constitutive promoter.

28. (Original) The system of claim 16, wherein the polynucleotide is comprised in a viral vector.

29. (Original) The system of claim 27, wherein the viral vector is an integrating viral vector.

30. (Original) The system of claim 28, wherein the integrating viral vector is a lentivirus, retrovirus, or adeno-associated virus.

31. (Original) The system of claim 16, further defined as comprising:

(a) a polynucleotide construct comprising a promoter operably linked to at least one polynucleotide encoding siRNAs;

(b) a polynucleotide encoding an inducible repressor that can repress the expression of said at least one siRNA;

(c) one or more vectors comprising the constructs of (a) and (b); and

(e) a compound or reagent that may be administered to the cell that controls the expression of the fusion protein.

32. (Original) The system of claim 31, further defined as comprising:

(a) a polynucleotide construct comprising a polymerase III-dependent promoter operably linked to at least one polynucleotide encoding siRNAs;

(b) a polynucleotide encoding a drug-inducible repressor fusion protein that comprises a DNA binding domain and a transcription repression domain; and

(c) a polynucleotide bindable by the binding domain of the fusion protein of (b) and positioned such that the transcription repression domain acts to repress transcription of the polynucleotide construct of (a);

(d) one or more vectors comprising the constructs of (a), (b), and (c); and

(e) a compound that may be administered to the cell that controls the expression of the fusion protein or that controls the binding of the fusion protein to the polynucleotide sequence bindable by the binding domain of the fusion protein.

33. (Original) The system of claim 32, wherein the polynucleotide encoding the fusion protein is operatively linked to an inducible promoter.

34. (Original) The system of claim 32, wherein the promoter is a constitutive promoter.

35. (Original) The system of claim 32, wherein the polynucleotide sequence bindable by the binding domain of the fusion protein is the tetracycline operator (*tetO*) sequence, the fusion protein of (ii) is comprised of the DNA binding domain of the tetracycline repressor (tTR) fused to the KRAB repression domain of human Kox-1 (tTR-KRAB), and the substance of (c) is doxycycline.

36. (Original) The system of claim 32, wherein the vector of (b) is a lentiviral vector, an MLV vector, an AAV vector, a plasmid vector or an adenoviral (Adv or Ad) vector.

37. (Original) The system of claim 35, wherein the polynucleotide sequence bindable by the binding domain of the fusion protein of (b), the promoter operably linked to the polynucleotide sequence encoding the siRNA and the polynucleotide sequence encoding the siRNA are comprised in the U3 region of the 3' long terminal repeat of the lentiviral vector.

38. (Original) The system of claim 32, wherein the polynucleotide encoding the fusion protein is comprised within a second, separate vector from the vector comprising the constructs of (a).

39. (Original) The system of claim 38, wherein the second vector comprising the polynucleotide encoding the fusion protein is a lentiviral vector, a MLV vector, an AAV vector, a plasmid vector or an adenoviral (Adv or Ad) vector.

40. (Original) The system of claim 15, wherein the polynucleotide encodes siRNA that forms a stem-and-loop structure, or a hairpin.

41. (Original) A mammalian cell comprising a polynucleotide construct in accordance with claim 1.

42. (Original) The mammalian cell of claim 41, further defined as comprising:

(a) a first polynucleotide sequence comprising a promoter operably linked to at least one nucleic acid segment encoding an siRNA;

(b) a second polynucleotide sequence encoding a conditional repressor fusion protein that comprises a DNA binding domain and a transcription repression domain; and

(c) a third polynucleotide sequence bindable by the binding domain of the fusion protein of (b) and positioned such that the transcription repression domain acts to repress transcription of the nucleic acid segment of (a).

43. (Original) The mammalian cell of claim 41, wherein the conditional repressor fusion protein is drug inducible.

44. (Original) The mammalian cell of claim 42, further comprising

(d) a fourth polynucleotide sequence, wherein the fourth polynucleotide sequence is excisable and prevents transcription from the polymerase III-dependent promoter; and,

(e) a fifth polynucleotide sequence encoding an enzyme capable of excising the fourth polynucleotide sequence, wherein the fifth polynucleotide sequence is under the control of a regulatable promoter.

45. (Original) The mammalian cell of claim 44, wherein the third polynucleotide sequence bindable by the binding domain of the fusion protein is the tetracycline operator (*tetO*) sequence, the fusion protein of (b) is comprised of the DNA binding domain of the tetracycline repressor (tTR) fused to the KRAB repression domain of human Kox-1 (tTR-KRAB), and the fusion protein is controlled by doxycycline.

46. (Original) The mammalian cell of claim 41, wherein the cell is an undifferentiated cell.

47. (Original) The mammalian cell of claim 41, wherein the cell is an oocyte or fertilized oocyte.

48. (Currently Amended) A transgenic animal having one or more cells as defined by any one of ~~claims 41—47~~ claim 41.

49. (Original) A method of creating a transgenic animal capable of exhibiting conditional knockdown of a target gene comprising:

a) introducing into a sex cell or an undifferentiated embryonic cell an expression construct comprising a polynucleotide in accordance with claim 1;

b) fertilizing the cell to create an embryo if the cell is a sex cell; and,

c) transplanting the embryo into a female animal, wherein the female animal produces a transgenic animal.

50. (Original) The method of claim 49, wherein the sex cell or undifferentiated embryonic cell is an unfertilized oocyte, a fertilized oocyte, an embryonic stem cell, a cell within a morula or blastocyst.

51. (Original) The method of claim 49, further comprising culturing the cell prior to introduction of the expression construct and/or transplantation.

52. (Original) A method of regulating the expression of a gene in a cell, the method comprising the steps of:

(a) preparing a polynucleotide construct in accordance with claim 1, wherein the siRNA encoded by said construct downregulates the expression of said gene;

(b) externally regulating the expression of the encoded siRNA through the externally controllable promoter.

53. (Original) The method of claim 52, wherein the externally controllable promoter is a repressible promoter whereby expression of the encoded siRNA can be downregulated by means of an externally applied agent.

54. (Original) The method of claim 53, wherein expression of the encoded siRNA can be downregulated by means of an externally applied drug.

55. (Original) The method of claim 53, wherein the repressible promoter comprises at least one *tetO* sequence.

56. (Original) The method of claim 52, wherein said method further comprises the step of providing a polynucleotide encoding an inducible repressor that can repress the expression of the siRNA.

57. (Original) The method of claim 56, wherein the polynucleotide encoding the repressor is further defined as a drug-controllable repressor fusion protein that comprises a DNA binding domain and a transcription repression domain, and wherein the binding domain of the fusion protein can bind the polynucleotide construct such that the trancription repression domain acts to repress transcription of the siRNA.

58. (Original) The method of claim 52, wherein the promoter regulating expression of the siRNA is a constitutive promoter.

59. (Original) The method of claim 52, wherein the promoter regulating expression of the siRNA is a tissue-specific promoter.

60. (Original) The method of claim 52, wherein said cell is further defined as being in a cell line.

61. (Original) The method of claim 59, wherein said method further comprises the step of providing to said cell a drug for testing drug function in the absence of a gene product encoded by said gene.

62. (Original) The method of claim 52, wherein said cell is comprised in an animal.

63. (Original) The method of claim 56, wherein the polynucleotide construct encoding the siRNA is further defined as being administered to a region of said animal, wherein the animal comprises said polynucleotide encoding the repressor.

64. (Original) The method of claim 63, wherein said administering is by injection.

65. (Original) The method of claim 63, wherein said region of the animal is in an organ.

66. (Original) The method of claim 62, wherein the animal is a human patient.

67. (Original) The method of claim 66, wherein the gene is an oncogene.

68. (Original) The method of claim 67, wherein the oncogene is ABLI, BLC1, BCL6, CBFA1, CBL, CSFIR, ERBA, ERBB, EBRB2, ETS1, ETS1, ETV6, FGR, FOX, FYN, HCR, HRAS, JUN, KRAS, LCK, LYN, MDM2, MLL, MYB, MYC, MYCL1, MYCN, NRAS, PIM1, PML, RET, SRC, TAL1, TCL3 or YES.

69. (Original) The method of claim 52, wherein externally regulating the expression of the encoded siRNA comprises administering an agent to the patient that effects an upregulation or downregulation of said expression.

70. (Original) The method of claim 69, wherein the agent is an antibiotic, radiation, steroid, hormone, metal, divalent cation, nutrient, or temperature.

71. (Original) The method of claim 70, wherein the radiation is ionizing radiation.

72. (Original) A method of controlling the ability of a cell to be recognized immunologically, comprising the steps of:

(a) obtaining a cell comprising:

(i) a polynucleotide construct in accordance with claim 1, wherein the siRNA encoded by said construct downregulates the expression of a polynucleotide encoding a transplantation antigen; and

(ii) a polynucleotide encoding an inducible repressor that can repress the expression of said siRNA; and

(b) externally regulating the expression of the encoded siRNA through the externally controllable promoter.

73. (Original) The method of claim 72, wherein said cell is in an animal.

74. (Original) The method of claim 72, wherein the transplantation antigen is an MHC I antigen.

75. (Original) The method of claim 72, wherein said transplantation antigen is beta2-microglobulin, an HLA, H-Y, P35B, Kdm4, Kdm5, TL, P198, P91A, or H-2Kb.

76. (Original) The method of claim 75, wherein said HLA antigen is HLA-C, HLA-G, or HLA-DQ.

77. (Original) The method of claim 74, wherein said cell is an islet cell, a stem cell, a hepatocyte, a dopaminergic neuron, or a keratinocyte.

78. (Original) A method of treating a disease condition amenable to treatment with an siRNA, the method comprising the steps of:

(a) preparing a polynucleotide construct in accordance with claim 1, wherein the siRNA encoded by said construct is for the treatment of the disease condition;

(b) externally regulating the expression of said siRNA through said externally controllable promoter.

79. (Original) The method of claim 78, wherein the disease is a hyperproliferative disorder.

80. (Original) The method of claim 79, wherein the hyperproliferative disorder is cancer.

81. (Original) The method of claim 80, wherein the cancer is gliosarcoma, breast cancer, lung cancer, brain cancer, melanoma, prostate cancer, ovarian cancer, pancreatic cancer, liver

cancer, colon cancer, cervical cancer, bladder cancer, spleen cancer, head and neck cancer, or bone cancer.

82. (Original) The method of claim 78, wherein the disease condition is hyperthyroidism.

83. (Original) The method of claim 78, wherein said disease condition is associated with a hypersecretion defect.

84. (Original) The method of claim 83, wherein the hypersecretion defect comprises a hormone hypersecretion defect.